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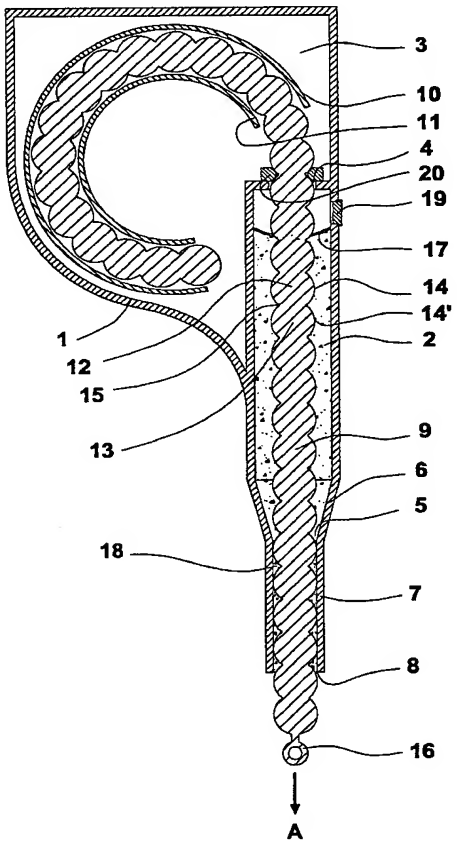
[Continued on next page]

(54) Title: MULTIPLE DOSE DISPENSER FOR POWDER INHALATORS AND CORRESPONDING METHOD OF DISPENSATION



(57) Abstract: A dispenser for a pulverous pharmaceutical composition for use with powder inhalators comprises a sealed housing (1) and a compartment (2) in the housing (1) for storing the composition. The storage compartment (2) further comprises an opening (5), a dispensing element (9) disposed in the storage compartment (2) and extending through the opening (5), an element (7) with a channel joined to the opening (5) externally of the compartment (2), and means for step-wise displacement of the dispensing element (9). The dispensing element (9) can be displaced towards the opening (9) and comprises sealing portions (14,14') of a diameter corresponding to the inner diameter of the channel spaced by dispensing portions (15) of substantially reduced diameter each of which holds a single dose of the composition.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

MULTIPLE DOSE DISPENSER FOR POWDER INHALATORS AND CORRESPONDING METHOD OF DISPENSATION

FIELD OF THE INVENTION

The present invention relates to a dispenser for a pulverous pharmaceutical composition or the like for use with powder inhalators, and a corresponding method of dispensation.

BACKGROUND OF THE INVENTION

The administration of pulverous pharmaceutical compositions to the lungs of patients suffering from asthma and other diseases is well known in the art. The inhalators used for dispensation may carry single or multiple doses of the composition. Multiple dosage inhalators are advantageous in terms of cost and convenience. A problem with such inhalators is the difficulty to reproducibly provide metered doses in a simple manner. This is due to the fact that often only very small amounts of composition have to be dispensed as a single dose which makes metering difficult. Another problem is that most compositions have to be protected from humidity prior to dispensation which necessitates sealing of the compartment where the dose(s) are stored.

One solution to this problem disclosed in the art is to provide a number of single doses each contained in a separate compartment which is individually sealed against the environment by a blister. The seal is broken only immediately prior to dispensation upon the compartment with the dose being moved in a dispensing position within the inhalator by, for instance, a drum turret mechanism.

Another solution disclosed in the art is the provision of the dose in a gelatine capsule with which the inhalator is loaded. Prior to dispensation the capsule is cut with a knife to free its contents. A third solution disclosed in the art comprises the provision of a bulk composition in a compartment of the inhalator from which aliquots are removed by a disk provided with dose chambers sliding past a window in the compartment wall, the doses in the chambers being exposed to an inhalation air flow in another portion of the inhalator. Still another solution disclosed in the art comprises a slightly compressed and therefore loosely cohering bulk composition from which aliquots are removed by a blade scratching its surface.

One major problem with repetitively dispensing metered single doses of small size (in the order of a few mg) resides in the difficulty of keeping the compartment sealed in which the composition is stored, while allowing metered doses to be dispensed therefrom when required in a simple manner.

OBJECTS OF THE INVENTION

An object of the present invention is to provide a dispenser of the aforementioned kind in which the pulverous medicament is stored in a single compartment that can be kept sealed while allowing metered doses to be dispensed therefrom on request in a simple manner.

Another object of the invention is to provide a process for repetitively dispensing metered doses of a pulverous medicament stored in a sealed single compartment in an inhalator or the like.

A further object of the invention is to provide a method of administering metered doses dispensed in such way to a patient.

Still another object of the invention is to provide an inhalator comprising a dispenser according to the invention.

Further objects of the invention will become evident from the following short description of the invention, the description of preferred embodiments thereof, and from the appended claims.

SHORT DESCRIPTION OF THE INVENTION

According to the present invention is disclosed a dispenser for a pulverous pharmaceutical composition for use with powder inhalators, comprising a housing sealed from the environment and a storage compartment for storing the composition disposed in the housing, the storage compartment having a first opening, further comprising a dispensing element of preferably rotationally symmetric shape disposed in the compartment and extending through said opening, an element with a preferably tubular channel joined to the opening disposed externally of the compartment, and means for step-wise displacement of the dispensing element, the dispensing element comprising, in an axial direction, sealing portions of a diameter corresponding to the inner diameter of said tubular channel element spaced by dispensing portions of substantially reduced diameter for holding single doses of the composition, the dispensing element being arranged displaceable in a direction from the compartment towards said opening.

More particularly, according to the present invention is disclosed a dispenser of the aforementioned kind wherein the storage compartment comprises a second opening disposed in the housing opposite to the first opening, the dispensing element also extending through said second opening.

It is preferred for the channel to have a longitudinal extension corresponding to the distance between the centres of two adjacent sealing portions, in particular between three of such portions or more.

It is preferred for the dispensing element to have a multitude of sealing portions and dispensing portions, in particular at least three sealing portions and two dispensing portions or more. It is to be understood that the number of sealing portions should always exceed the number of dispensing portions by one. It is particularly preferred for the dispensing element (and, by necessity, the channel) to be rotationally symmetric.

It is preferred for the compartment to be of substantially cylindrical shape and for the first and second openings, in particular for the first opening, to be centred on the corresponding cylinder axis.

According to an advantageous aspect of the invention is provided a means for confining the pulverous medicament in a portion of the compartment extending from the opening or first opening, respectively, arranged displaceably in the direction of the opening or first opening, respectively, by the action of the dispensing element. It is advantageous to include guiding elements in the

compartment for directing the pulverous composition towards the dispensing element.

It is preferred for the compartment to have a further opening, which can be accessed from outside for filing with the composition, and can be permanently sealed upon the compartment having been filled.

According to the present invention is also provided a process for dispensation of multiple doses of a pulverous pharmaceutical composition in an inhalator, comprising:

- providing a pulverous pharmaceutical composition stored in a compartment of a dispenser, the compartment being in communication with a channel, the dispenser comprising a dispensing element disposed in the compartment and extending through the channel and sealing against the walls of the channel, the dispensing element being provided with sealing portions inter-spaced by dispensing portions;
- displacing, in a single step, the dispensing element in the direction of the channel by a distance corresponding to the distance between the centres of two adjacent sealing portions, the dispensing portion intermediate between said adjacent sealing portions thereby carrying a metered dose of said composition into the channel,
- further step-wise displacing said dispensing portion with said metered dose through the channel and out of the other end of the channel;
- contacting said metered dose disposed outside the other end of the channel with an air stream to form an aerosol for inhalation.

According to the present invention is also provided an inhalator comprising the dispenser of the invention.

According to the present invention is furthermore provided a method of administering single doses of a pulverous medicament to the lungs of a patient by use of the dispenser according to the invention in an appropriate inhalator.

SHORT DESCRIPTION OF THE DRAWINGS

In the following the invention will be described in greater detail by reference to a rough drawing illustrating in

Fig. 1 a first embodiment of the dispenser according to the invention, in a sectional view;

Fig. 2 the bead chain of the embodiment in Fig. 1, modified, in a partial view otherwise corresponding to the view of Fig. 1

Fig. 3 a second embodiment of the dispenser according to the invention incorporated in an inhalator, in a partial view otherwise corresponding to the view of Fig. 1;

Fig. 4. the embodiment of Fig. 3, in a full view otherwise corresponding to that of Fig. 3, reduced;

Fig. 5 the dispenser only of the embodiment of Figs. 3 and 4, in a full view corresponding to that of Fig. 4.

DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

The preferred embodiment of a dispenser for a pulverous pharmaceutical composition for use with powder inhalators shown in Fig. 1 comprises a housing 1 and a compartment 2 for storage of the composition arranged in the housing 1, the compartment 2 being shown in the Figure in a state nearly fully filled with composition. The housing including the compartment walls are made of a suitable polymer material, such as polypropylene or polystyrene, by pressure moulding or any other suitable technique, the compartment 2 being made in one piece with other portions of the dispenser. The housing 1 has the contour shown in Fig. 1 and a thickness of about 10-15 mm in a direction perpendicular to the section of Fig. 1, whereas the composition storage compartment 2 is of substantially cylindrical shape with a corresponding diameter, and has two openings 4,5 centred at the cylinder axis. The second or rear opening 4 is located in the rear wall of the compartment 3. Thereby the composition storage compartment 2 is in communication with the remaining inner space of the housing 1 termed chain reservoir compartment 3. The first or outlet opening 5 is spaced from the cylindrical main portion of the composition storage compartment 2 by a conical portion 6 narrowing towards the opening 5 to which is joined a short tube 7 having a front opening 8. A filling opening through which the composition storage compartment 2 can filled with the composition is provided near the rear end of the compartment 1; upon filling it is permanently sealed with a plug 19. A bead chain 9 made of nylon is disposed in the composition storage compartment 2 and extends from its outlet 5 opening through the tube 7 and out of the front opening 8. In the other direction the bead chain 9 extends through the rear opening 4 into the

chain reservoir compartment 3 in which a substantial portion of the bead chain 9 is stored in a rolled-up position between two guide rails 10,11. The diameter of the beads 12,13 perpendicular to the longitudinal axis of the bead chain 9 corresponds to the inner diameter of the tube 7 thus providing a seal with respective adjacent sealing portions 14;14'. The throat 15 between the two adjacent sealing portions 14,14' and the portion of the inner wall of tube 7 facing the throat 15 defines the volume of a single dose of the composition. It should be understood that opening 8 is the only opening in the housing 1 remaining upon filling the compartment 2 with the pulverous composition and sealing the filling opening with the plug 19.

A thin circular plate 17 of a flexible and resilient polymer material such as synthetic rubber is initially disposed at the rear of the compartment 2 between the filling hole and the second hole 4. The plate 17 has a central opening allowing the bead chain 9 to slide through but not without meeting some resistance which is sufficient to displace the plate 17 in a forward direction (a direction towards the outlet 5) in a way such as to keep the pulverous pharmaceutical composition in a slightly compressed state. At its front end extending from the housing the bead chain 9 has a rod end with 16 with an eye for displacing the bead chain in a direction away from the tube 7 indicated by arrow A.

The housing is made in two mirroring halves of which the section shown in Fig. 1 corresponds to faces at which the halves are joined after positioning the bead chain 9 in-between them. The halves can be joined by gluing or welding or any other appropriate technique.

A simple snap mechanism to provide for step-wise displacement of the bead chain 9 is arranged at the opening 4 in the reservoir compartment 3 in form of a perforated disk 20 of a resilient polymer material surrounding the bead chain. The diameter of the perforation is less than the diameter of the beads but can be made to widen to that diameter by application of an expanding force, such as the force exerted by the bead chain when being pulled in the direction of arrow A.

A section of another bead chain 21 with a different useful profile is shown in Fig. 21. This is just one example for a multitude of conceivable useful profiles.

The process for dispensation of multiple doses of a pulverous medicament in an inhalator by the dispenser described in the foregoing comprises the following steps. The assembled dispenser is filled with the pulverous pharmaceutical composition through the filling opening which then is closed by plug 19.

Single doses are removed from the composition stored in the storage compartment 2 by throat portions of the bead chain 9 being made to enter the tube 7. The volume of a single dose is that contained in the annular space 18 defined by the faces of a throat and the inner wall section of the tube 7 facing them. Step-by-step each dose is transported through the tube and released at its other end in an area with vigorous air flow. Thereby it produces an aerosol suitable for administration to the airways of a patient. The transport is in steps of a length corresponding the distance of the centres of two neighbouring beads 12,13 which corresponds to the distance between (the centres) of two neighbouring sealing portions

(14,14'). A suitable snap mechanism (not shown in the Figures) is provided for this step-wise movement. The front end of the bead chain 9 can be rolled up within the inhalator by a mechanism (not shown) or the front end of the chain can be made to extend out of the inhalator to be drawn out step-wise by the patient against the resistance of the aforementioned snap mechanism.

The dispenser of the invention can be easily adapted to fit various inhalators of known design. It is a sort of medicament magazine or cartridge for powder inhalators the useful life of which thereby can be substantially extended. Since there is only one sealed opening a negative pressure may build up in the dispenser by material (composition and beads) being removed from it. This effect can be countered by substantially reducing the wall thickness of part of the reservoir compartment 3 to allow it to bulge inwards.

A second embodiment of a dispenser according to the invention is shown in Figs. 3-5. In this embodiment the dispenser is integrated in an inhalator which resembles a pen and can be unobtrusively carried by the patient. Same reference numbers +100 designate elements corresponding to those of the first embodiment of Figs. 1-2. In this second embodiment the bead chain of the first embodiment has been exchanged for a straight dispensing element 109 which extends from a reservoir compartment 103 through a first opening at 104' to a composition storage compartment 102 and from there through a channel in front section 107 corresponding to the tube of the first embodiment into a narrow air passage 139, and from there through an opening in the opposite wall of the air passage 139 to a pocket 135 in which the terminal bead 134 can be cut off by a

knife 136, after which it can be removed through the opening of the pocket 135. The mechanism for step-wise displacement of the dispensing element is not shown in Figs. 4 and 5. The inhalator comprises a mouthpiece 138 with an opening 137 narrowing in the direction of the passage 139 which widens at its other end to an air bolus compartment 133 closed against the environment at opening 130 by a flap valve 131. The flap valve 131 is loaded by a spring (not shown) which delays the inwardly swivelling of the valve 131 around bearing 132 upon air being sucked in through the mouthpiece 138 until the negative pressure in the air bolus compartment 137 reaching a predetermined level corresponding to the loading spring force. The sudden air stream in the direction of the mouthpiece flowing through the passage 139 will carry with it the pulverous material contained in the recesses (throats) of the dispensing element 109 of which one is disposed in the passage as evident from Fig. 3.

C l a i m s

1. A dispenser for a pulverous pharmaceutical composition for use with powder inhalators, comprising a housing (1) sealed from the environment and a storage compartment (2;120) for storing the composition disposed in the housing (1), the storage compartment (2;120) having a first opening (5), further comprising a dispensing element (9;109) of preferably rotationally symmetric shape disposed in the compartment (2;120) and extending through said opening (5), an element (7;107) with a preferably tubular channel joined to the opening (5) and disposed externally of the compartment (2;120), and means for step-wise displacement of the dispensing element (9;109), the dispensing element (9;109) comprising, in an axial direction, sealing portions (14,14') of a diameter corresponding to the inner diameter of said channel element (7;107) spaced by dispensing portions (15) of substantially reduced diameter for holding single doses of the composition, the dispensing element (9;109) being arranged displaceable in a direction from the compartment (2;102) towards said opening (5).

2. The dispenser of claim 1, wherein the storage compartment (2;102) comprises a second opening (4; at 104') disposed in the housing (1) opposite to the first opening (5), the dispensing element (9;109) also extending through said second opening (4; at 104').

3. The dispenser of claim 1 or 2, wherein the channel has a longitudinal extension corresponding to the distance between the centres of two adjacent sealing portions (14,14') or more.

4. The dispenser of claim 1 or 2, wherein the channel element has a longitudinal extension corresponding to the distance between the centres of three adjacent sealing portions or more.

5. The dispenser of any of claims 1 to 4, wherein the dispensing element (9;109) has a multitude of sealing portions (14,14') and dispensing portions (15), with the proviso that the number of sealing portions (14,14') exceeds the number of dispensing portions (15) by one.

6. The dispenser of claim 1, wherein the storage compartment (2) is of substantially cylindrical shape and the opening (5) is centred on the corresponding cylinder axis.

7. The dispenser of claim 2, wherein the storage compartment (102) is of substantially cylindrical shape and the first and second (at 104') openings are centred on the corresponding cylinder axis.

8. The dispenser of any of claims 1 to 7, comprising means (20) for step-wise displacement of the dispensing element (9).

9. The dispenser of claim 1, comprising a means (17) for confining the pulverous medicament in a portion of the compartment extending from the opening (5), the means (17) being arranged for displacement in the direction of the opening (5) by the dispensing element (9).

10. The dispenser of claim 2, comprising a means (17) for confining the pulverous medicament in a portion of the compartment extending from the first opening (5), the

means (17) being arranged for displacement in the direction of the first opening (5) by the dispensing element (9).

11. The dispenser of any of claims 1 to 10, comprising a permanently sealable further opening which can be accessed from outside for filling of the storage compartment (2) with the pulverous pharmaceutical composition.

12. A process of dispensation of multiple doses of a pulverous pharmaceutical composition in an inhalator, comprising:

- providing a pulverous pharmaceutical composition stored in a compartment (2;102) of a dispenser, the compartment being in communication with a channel, the dispenser comprising a dispensing element (9;109) disposed in the compartment (2:102) and extending through the channel and sealing against the walls of the channel, the dispensing element (9;109) being provided with sealing portions (14,14') inter-spaced by dispensing portions (15);
- displacing, in a single step, the dispensing element (9;109) in the direction of the channel by a distance corresponding to the distance between the centres of two adjacent sealing portions (14,14'), the dispensing portion (15) intermediate between said adjacent sealing portions (14,14') thereby carrying a metered dose of pulverous medicament into the channel,
- further step-wise displacing said dispensing portion (9;109) with said metered dose of composition through the channel and out of the other end of the channel;

- contacting said metered dose disposed outside the other end of the channel with an air stream to form an aerosol for inhalation.

13. An inhalator comprising the dispenser according to any of claims 1 to 11.

14. A method of administering single doses of a pulverous medicament to the lungs of a patient comprising the process of dispensation according to claim 12.

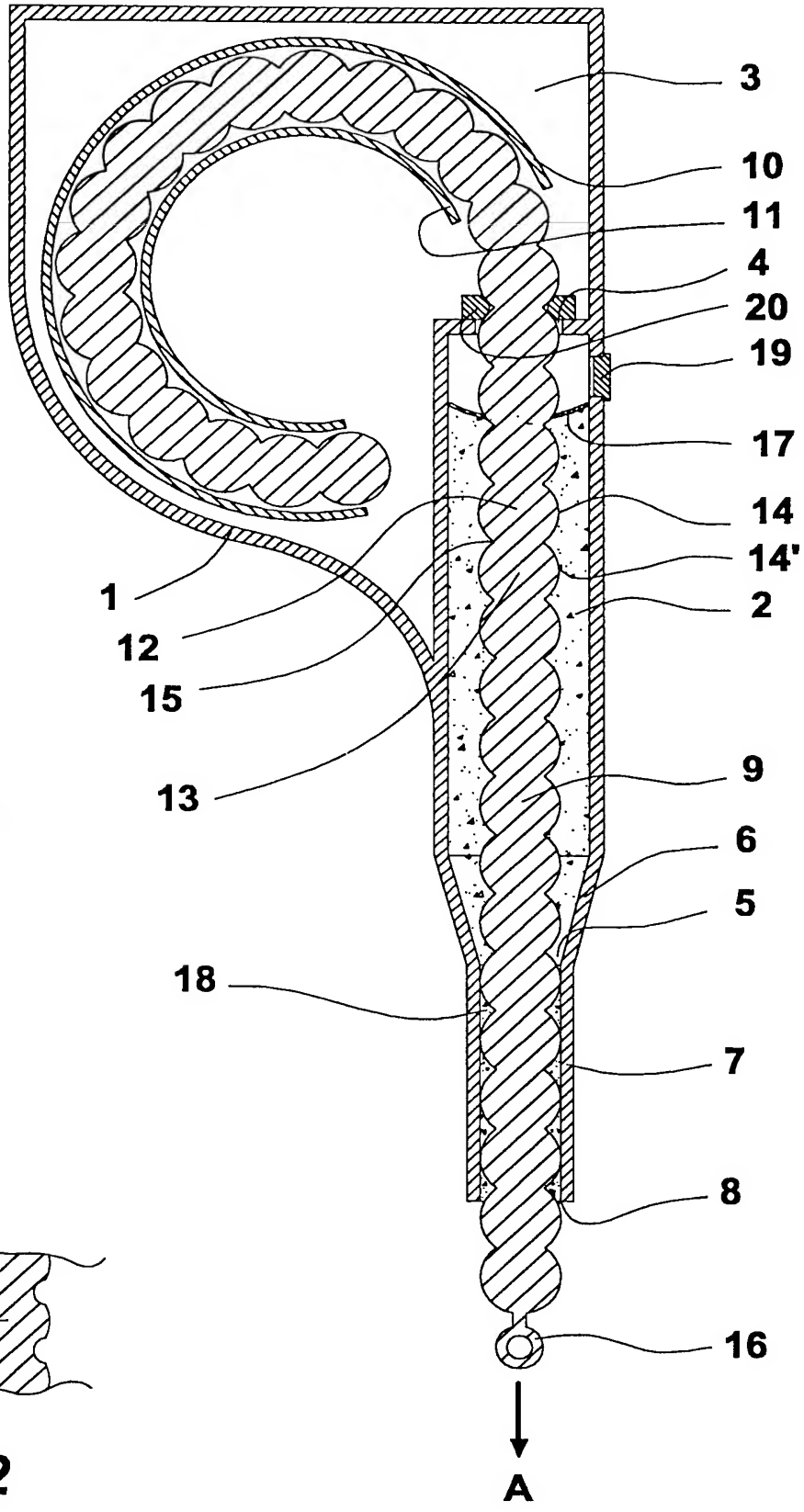

Fig. 1

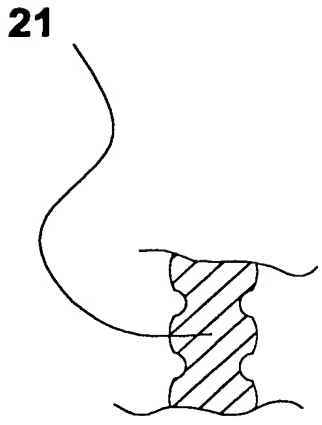

Fig. 2

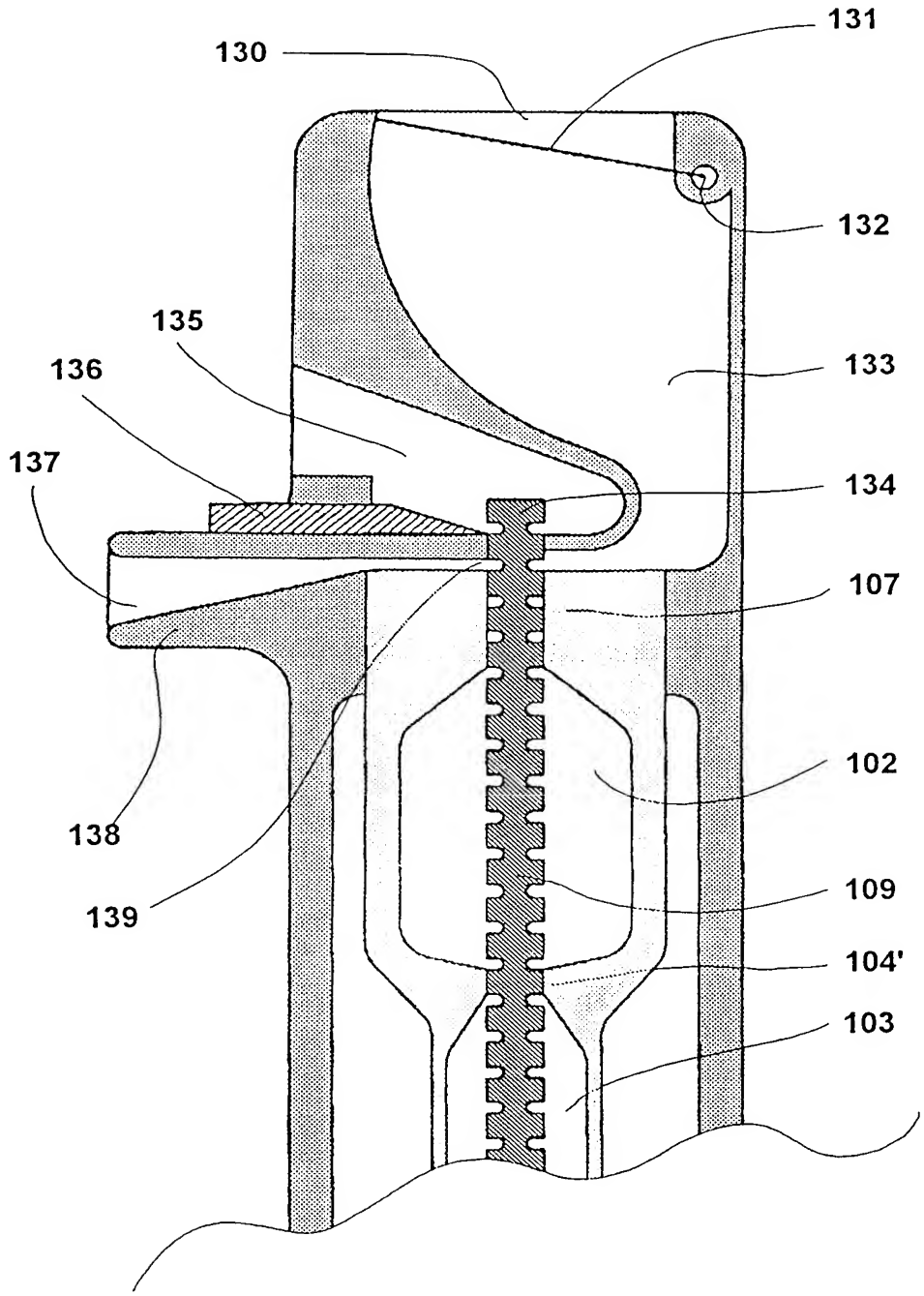

Fig. 3

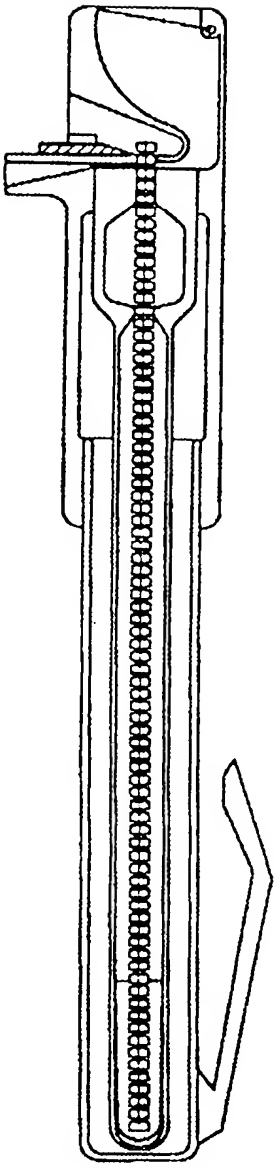

Fig. 4

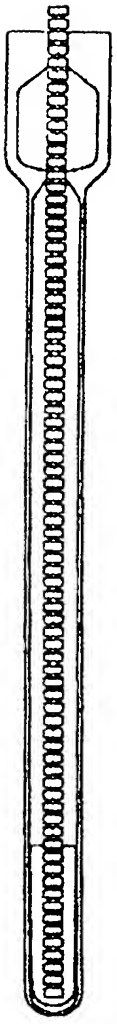

Fig. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02049

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61M 15/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0467172 A1 (PROMO PACK SA), 22 January 1992 (22.01.92) --	1-13
A	WO 9422515 A1 (FISONS PLC), 13 October 1994 (13.10.94) --	1-13
A	US 4117844 A (MICHAEL JAMES), 3 October 1978 (03.10.78) --	1-13
A	US 5634900 A (YUJI MAKINO ET AL), 3 June 1997 (03.06.97) --	1-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2001	13-02-2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Jack Hedlund/Els Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02049

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **14**
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/12/00

International application No.
PCT/SE 00/02049

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INTERNATIONAL SEARCH REPORT

Information on patent family members

27/12/00

International application No.
PCT/SE 00/02049

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